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Vancomycin hypersensitivity

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Last literature review version 19.1: January 2011 | **This topic last updated:** June 14, 2010

INTRODUCTION — [Vancomycin](#) causes several different types of hypersensitivity reactions, ranging from localized skin reactions to generalized cardiovascular collapse. However, the most frequent adverse reaction, the "red man syndrome," is a rate-dependent infusion reaction, and not a true allergic reaction. Vancomycin may also elicit several other types of cutaneous and systemic reactions.

[Vancomycin](#) hypersensitivity will be reviewed here. Other antibiotics that commonly cause hypersensitivity reactions include the beta-lactam antibiotics and sulfonamides, and hypersensitivity reaction to these drugs are presented separately. (See "[Allergy to penicillins](#)" and "[Sulfonamide allergy in non HIV-infected patients](#)".)

RED MAN SYNDROME — The most common adverse reaction to [vancomycin](#) is "red man syndrome" (RMS), which also may be called "red neck syndrome." RMS is not thought to involve drug-specific antibodies and may develop even with the first administration of vancomycin. RMS is a form of pseudoallergic drug reaction, or an adverse drug reactions with signs and symptoms that mimic immunologic drug allergies, but in which immunologic mechanisms have not been demonstrated.

Signs and symptoms — RMS is characterized by flushing, erythema, and pruritus, usually affecting the upper body, neck, and face more than the lower body. Pains and muscle spasms in the back and chest, dyspnea, and hypotension may also occur [[1,2](#)]. Hypotension in isolation has been reported [[3](#)].

RMS is rarely life-threatening, although severe cardiovascular toxicity and even cardiac arrest have been reported [[3,4](#)]. IgE-mediated anaphylaxis can present with symptoms similar or identical to those of severe RMS, requiring that clinicians be mindful of this alternative diagnosis. (See '[IgE-mediated anaphylaxis](#)' below.)

Mechanism — RMS is best classified as an idiopathic infusion reaction which resembles IgE-mediated anaphylaxis, but does not involve drug-specific IgE. Studies in animals indicate that [vancomycin](#) directly activates mast cells, resulting in release of vasoactive mediators, such as histamine [\[5,6\]](#). In several human reports, elevations in serum histamine were found to be related to the clinical severity of RMS [\[7-9\]](#). At least one study, however, documented RMS without detectable elevations in plasma histamine, suggesting either that other mediators may be involved [\[10\]](#), or that plasma histamine is not a sufficiently sensitive marker for mast cell activation localized to the skin.

Relationship to infusion rate — RMS is a rate-related infusion reaction in most instances. The infusion rate of 33 mg/min (1 gram over 30 minutes) causes RMS symptoms in most subjects, whereas slower rates of 10 mg/min (corresponding to 1 gram over 1.67 hours) or less rarely cause symptoms [\[11\]](#). Thus, to avoid RMS, [vancomycin](#) should be infused over a minimum of 100 minutes or at a rate no higher than 10 mg/min, whichever results in a slower infusion.

The following studies illustrate the relationship of RMS to infusion rate [\[7,12,13\]](#):

- One study of 10 adult male volunteers compared the incidence and severity of RMS resulting from the infusion of 1 gram of [vancomycin](#) over one or two hours [\[7\]](#). The one hour infusion resulted in 8 of 10 subjects developing RMS (three mild, three moderate, and two severe), whereas the two hour infusion resulted in 3 of the 10 subjects developing symptoms (all mild).
- In studies of inpatients with serious infections, however, fewer than 10 percent developed RMS following 1 gram infused over one hour, indicating that patients vary in their susceptibility to this reaction [\[8,10\]](#).
- In another study, 10 healthy presurgical patients received rapid infusions of 1 gram of [vancomycin](#) over 10 minutes [\[12\]](#). All developed RMS: seven and three had severe and mild cutaneous reactions, respectively, and five experienced a reduction in blood pressure of 20 percent or more, necessitating discontinuation of the infusion.

Predisposing medications — Mast cells may be more easily activated by [vancomycin](#) when certain other medications are also present. The combination of vancomycin and opioids (eg, [morphine](#), [meperidine](#), [codeine](#)) enhances dose or rate-related mast cell degranulation [\[14\]](#). There is a bidirectional synergism that occurs between vancomycin and the opioids in the induction of adverse effects. Adverse reactions can occur following administration of vancomycin in individuals with prior opiate administration, or conversely, in those receiving opioids with prior vancomycin administration [\[15\]](#).

Similar interactions could theoretically occur between [vancomycin](#) and radiocontrast dye, some smooth muscle relaxants used in general anesthesia, and any other agents that potentiate mast cell degranulation.

These agents should not be administered simultaneously with [vancomycin](#) when possible ([table 1](#)).

Prevention of initial reactions — Empiric premedication to prevent RMS is not usually necessary for most patients who are receiving [vancomycin](#) for the first time at standard rates of infusion (≤ 10 mg/min). We generally do not administer premedication for doses ≤ 500 mg given over one hour, or doses of 500 mg to 1 gram, given over two hours. However, we advise even slower rates of infusion for patients who are also receiving opioids or other medications that predispose to mast cell activation. (See '[Predisposing medications](#)' above.)

In contrast, empiric premedication with antihistamines is commonly employed if more rapid infusions of [vancomycin](#) are required in emergency or presurgical settings. There is evidence that pretreatment with antihistamines is effective in reducing the incidence and severity of RMS, although the optimal regimen has not been determined:

- A small randomized trial of 33 patients found that pretreatment with [diphenhydramine](#) (50 mg orally) completely prevented RMS in a group of patients receiving 1 gram of [vancomycin](#) over 60 minutes [8]. Reactions occurred in 47 percent of the placebo group, compared to none in the diphenhydramine group.
- In another randomized study of very rapid infusions (1 gram over 10 minutes) in 30 presurgical patients, oral premedication with both H1 and H2 antihistamines reduced the incidence and severity of RMS, although symptoms still occurred in some individuals [12]. This study employed oral [diphenhydramine](#) (≤ 1 mg per kg) plus oral [cimetidine](#) (≤ 4 mg per kg), given one hour before infusion. Hypotension developed in 50 percent of placebo patients, and none in the antihistamine group, although one antihistamine-treated patient had intolerable itching and could not complete the infusion.
- The same investigators performed another randomized trial in 40 patients, using the same medications, doses, and setting, although the antihistamine premedications ([diphenhydramine](#) and [cimetidine](#)) were administered intravenously [16]. Hypotension developed in 11 and 63 percent of antihistamine- and placebo-treated patients, respectively. Cutaneous findings developed in 63 and 100 percent of antihistamine and placebo-treated patients, respectively, and itching was severe enough in two antihistamine-treated patients to necessitate discontinuation of the infusion.

Based upon these limited studies, premedication with H1 alone may be sufficient to prevent RMS following mildly increased rates of infusion, although even the combination of H1 and H2 antihistamines did not completely prevent RMS following very rapid infusions of [vancomycin](#). Oral and intravenous antihistamine premedications appear to be similarly efficacious.

Thus, we suggest empiric premedication for patients receiving [vancomycin](#) at increased rates of infusion (ie, rates exceeding 10 mg/min or 1 gram over one hour). Oral administration of premedications is preferred when possible. Although H1 antihistamines may be sufficient for mildly increased infusion rates, we suggest administration of both an H1 and H2 antihistamine to minimize the likelihood of a reaction if significantly faster rates are used.

Management of acute RMS — The optimal management of RMS has not been determined in controlled trials. The approach outlined herein is based on the authors' clinical experience.

- For mild to moderate reactions (eg, the patient is uncomfortable due to flushing or pruritus, but hemodynamically stable and not experiencing chest pain or muscle spasm), we typically interrupt the infusion, treat with [diphenhydramine](#) (50 mg orally or intravenously), and [ranitidine](#) (50 mg intravenously). Symptoms usually subside promptly. The infusion can then be restarted at one-half the original rate.
- For severe reactions (eg, involving muscle spasm, chest pain, or hypotension) we stop the infusion, treat with [diphenhydramine](#) (50 mg intravenously) as well as [ranitidine](#) (50 mg intravenously), and IV fluids if hypotension is present. Once symptoms have resolved, the infusion can be restarted, and given over four or more hours. For future doses in such patients, we suggest repeat premedication with antihistamines before each dose and infusion over four hours.

Following RMS of any severity, the patient's medication list should be reviewed to determine if other predisposing medications (eg, opiates) can be identified and discontinued, before restarting the infusion.

Recurrent reactions — Some individuals experience recurrent and persistent symptoms, despite premedication and slower infusion rates [8,15,17]. These individuals may have mast cell and/or basophils that are easily activated. Desensitization can be attempted in such patients if [vancomycin](#) is absolutely required. (See '[Desensitization](#)' below.)

IGE-MEDIATED ANAPHYLAXIS — Anaphylaxis is an immunologically-mediated reaction involving drug-specific IgE antibodies. Anaphylaxis in response to [vancomycin](#) administration is believed to be rare, although reactions involving angioedema, respiratory distress, and bronchospasm, with demonstrable

drug-specific IgE have been described [17-19]. (See "[Anaphylaxis: Rapid recognition and treatment](#)".)

Clinical manifestations — Anaphylaxis usually does **not** occur on the first administration of the medication because prior exposure to the drug is necessary to form drug-specific IgE antibodies. Patients with anaphylactic reactions to [vancomycin](#) often have a history of multiple prior exposures.

The symptoms of anaphylaxis include, (but are not limited to) urticaria, angioedema, generalized pruritus, tachycardia or bradycardia, hypotension, cardiac arrhythmias, nausea and vomiting, headache, lightheadedness, and hypotension ([table 2](#)).

Wheezing and respiratory distress are more common in anaphylaxis than in severe RMS, whereas RMS more typically presents with chest pains causing a sensation of chest tightness. Angioedema is usually seen in anaphylaxis only. However, it may not be possible to distinguish anaphylaxis from severe RMS based upon clinical presentation. The patient should be assumed to have anaphylaxis in such cases and managed accordingly.

Acute management — If anaphylaxis is suspected, the infusion should be stopped immediately and the patient should be treated with intramuscular epinephrine. Overviews of the treatment of anaphylaxis in adults and in children (with medication doses) are provided in the tables ([table 3](#) and [table 4](#)). A more detailed discussion of the treatment of anaphylaxis is presented separately. (See "[Anaphylaxis: Rapid recognition and treatment](#)".)

Serum tests and skin tests — It would be desirable to be able to distinguish RMS from IgE-mediated anaphylaxis to avoid falsely labeling a patient as allergic or discontinuing the drug unnecessarily. Unfortunately, serum and skin tests cannot reliably discriminate between these two reactions. In addition, skin testing has not been validated. Thus, differentiating between anaphylaxis and severe RMS is usually based upon clinical signs and symptoms.

- Serum tests - Elevations in these mast-cell derived mediators are variably found in IgE-mediated anaphylaxis, although normal levels do not exclude anaphylaxis. One study of anaphylactic and anaphylactoid reactions to various agents during anesthesia demonstrated that serum elevations in mast cell tryptase did not reliably predict which patients would have positive skin tests to the medications involved, although skin-test positive patients tended to have elevated tryptases more often [[20](#)].

Plasma histamine or serum tryptase levels have been studied in severe reactions to [vancomycin](#) [[20-26](#)]. As reviewed previously, multiple studies have found a

correlation between elevated plasma histamine and the severity of RMS [8,11]. Histamine, therefore, cannot be used to distinguish anaphylaxis from severe RMS.

Tryptase is stored preformed within mast cell granules and released during mast cell degranulation. One study found that tryptase levels were not significantly elevated in severe RMS reactions, even when histamine levels were increased [21]. However, this study examined blood samples collected 10 minutes after infusion, and may have missed later elevations. In addition, tryptase is not consistently elevated in drug-induced anaphylaxis either, and tryptase levels have not been measured in reports of [vancomycin](#) anaphylaxis.

- Skin testing - Skin testing with [vancomycin](#) has not been validated, and the positive and negative predictive value of the results are not known. However, isolated case reports described reactions that were highly suggestive of IgE-mediated drug allergy, in which skin testing correlated with clinical reactivity. As an example, one patient developed generalized urticaria and respiratory distress after several doses of vancomycin [18]. Intradermal skin tests were positive at 0.1 mcg/mL, whereas control subjects reacted at >10 mcg/mL. The patient was desensitized over 13 days, after which repeat skin testing was negative. Another case report also documented conversion to a negative skin test following desensitization [27].

These reports suggest that skin testing with appropriate [vancomycin](#) concentrations may reflect clinical reactivity and provide supportive evidence for clinical impressions. A positive skin test at concentrations of 1 mcg/mL or lower is strongly suggestive of drug allergy, in the setting of an appropriate clinical history.

Use of alternate medications — Other antimicrobial agents should be considered for patients who have experienced very severe symptoms in response to [vancomycin](#). Some patients receive vancomycin because of a reported history of allergy to penicillins, yet penicillin may be a superior antibiotic for certain infections, such as native valve endocarditis due to methicillin sensitive *Staphylococcus aureus* (see "[Antimicrobial therapy of native valve endocarditis](#)").

Patients are sometimes labeled as penicillin-allergic based on a vague past history, or may have lost the allergy over time. Presurgical evaluation by an allergy specialist to confirm or exclude penicillin allergy should be arranged whenever possible. Several studies have demonstrated the value of avoiding [vancomycin](#) for surgical prophylaxis in patients with a self-reported history of penicillin allergy [28-30](see "[Allergy to penicillins](#)").

There are limited antibiotic options for certain infections, however, such as methicillin-resistant *Staphylococcus aureus*, coagulase-negative staphylococci, and ampicillin-resistant enterococci. Alternative agents are discussed in detail in specific

topic reviews. (See ["Treatment of invasive methicillin-resistant Staphylococcus aureus infections in adults"](#) and ["Coagulase-negative staphylococci: Antimicrobial resistance and treatment"](#) and ["Treatment of enterococcal infections"](#).)

Teicoplanin has the same spectrum of antimicrobial activity as [vancomycin](#), although this medication is currently not available in the United States. Rare case reports describe patients with flushing and pruritus or vasculitis in response to both vancomycin and teicoplanin, raising the possibility of cross-reactivity [[31,32](#)]. Overall, however, the incidence of adverse effects with teicoplanin is lower [[33-35](#)].

Desensitization — When no other antimicrobial of equivalent efficacy is available, the readministration of [vancomycin](#) to a patient with a past severe RMS or possible anaphylaxis may need to be considered. Vancomycin desensitization is appropriate in this setting. Desensitization to vancomycin has been successfully performed for both suspected IgE-mediated reactions and for severe RMS that was refractory to the measures outlined above [[15,18,27,36,37](#)].

Desensitization is most commonly used in allergic reactions to various antibiotics that are due to true IgE-mediated mechanisms. Desensitization induces clinical "tolerance" to an agent when IgE-mediated mechanisms are responsible; the mechanism by which desensitization might work in non-IgE mediated reactions is not known. (See ["Allergy to penicillins"](#).)

Precautions — Desensitization, or any form of reexposure, is strictly CONTRAINDICATED in patients with the following types of past reactions:

- Exfoliative skin reactions: reactions involving blistering, peeling, or sloughing of the skin, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. (See ["Stevens-Johnson syndrome and toxic epidermal necrolysis: Management, prognosis, and long-term sequelae"](#).)
- DRESS (drug rash eosinophilia with systemic symptoms) syndrome, also called the drug-induced hypersensitivity syndrome (DiHS) [[38,39](#)]. (See ["Drug allergy: Classification and clinical features"](#).)

Consultation with an allergy specialist experienced in adverse drug reactions is recommended if desensitization is under consideration. Precautions regarding desensitization include the following:

- These procedures are performed immediately before required treatment.
- Other concurrent health issues should be as well controlled as possible, particularly cardiopulmonary conditions.
- Patients should optimally not be taking medications that may increase the

likelihood of anaphylaxis or interfere with treatment of anaphylaxis, such as ACE-inhibitors or beta-blockers.

- Desensitizations should be performed in an appropriate medical setting, with proper monitoring in place, and immediate availability of rescue medications and equipment. Desensitizations for IgE-mediated sensitivities to intravenous medications are usually performed in an intensive care unit.
- Documentation of informed consent, including a thorough discussion of risks and benefits of the procedure, is essential.

Protocols — A variety of intravenous protocols have been employed [40]. Some call for intermittent doses that increase incrementally over periods ranging from 2 to 13 days [18,27]. Other protocols can be completed in a period of several hours, and these are generally preferred, as patients are often infected and acutely in need of treatment [15,36,40-42].

A protocol that can be completed in several hours is provided (table 5) [40]. Studies comparing the success rates of different protocols have not been performed (table 6).

Symptoms during desensitization — Symptoms during desensitization have been noted in as many as 30 percent of cases. Most can be managed without discontinuation of the desensitization protocol. Symptoms are usually mild (eg, flushing, pruritus, limited urticaria). These are managed by halting the infusion and treating the symptoms that do not subside spontaneously (table 7). Once symptoms have subsided, the last tolerated step is repeated. This "stepping back" may be performed again if needed, or an intermediate step can be inserted after the last tolerated step, and before the problematic step by reducing the infusion rate of the problematic step.

If moderate or severe symptoms develop, the infusion should be halted and the symptoms treated. The decision to proceed with desensitization depends upon the patient's status and need for [vancomycin](#) (table 7).

There is one report of a patient who failed a rapid protocol and was subsequently successfully desensitized using a 13 day procedure [27].

Duration of efficacy — Desensitization is believed to induce a temporary state of tolerance, allowing the drug to be administered safely as long as the patient remains continually exposed to it. Once the initial desensitization is complete, the patient can receive subsequent doses normally, and no symptoms are anticipated. Serum levels of [vancomycin](#) must be monitored carefully to ensure that the concentration in the blood does not drop below detectable levels [19,43]. It is not known what threshold level of drug is required to maintain the tolerized state,

however, the drug levels should be kept within the therapeutic range if possible, both to maintain tolerance and treat the infection. This may require continuous rather than intermittent dose infusions.

If the drug level does become undetectable, then desensitization should be repeated in order to reintroduce the medication safely. Once the course of treatment is completed, it must be clearly explained to patients that they still have an allergy to [vancomycin](#) and would have to be desensitized again if it were required in the future.

OTHER FORMS OF HYPERSENSITIVITY — The most common hypersensitivity reaction is skin rash, although other reactions, including hematologic and renal disorders, drug fever, and phlebitis can also occur [\[44,45\]](#). Desensitization should not be attempted following any of these reactions.

Systemic — Both [vancomycin](#) and teicoplanin have elicited the development of the DRESS (drug rash with eosinophilia and systemic symptoms) syndrome (also called DiHS) [\[38,46,47\]](#). Cross-sensitivity to both drugs is possible, as described in at least one case report [\[38\]](#). This syndrome includes rash, atypical lymphocytosis, frequent but not uniform eosinophilia, and often lymphadenopathy. There may be hepatic, renal and/or pulmonary involvement. Treatment involves discontinuing the causative drug, and conventionally, administration of glucocorticoids [\[39,47\]](#). The culprit drug should be avoided in the future, as rechallenge can precipitate severe and fatal reactions.

Dermatologic — Maculopapular or urticarial skin eruptions are the most frequent dermatologic manifestations of [vancomycin](#) hypersensitivity.

Vancomycin-related linear IgA bullous dermatosis — A rare, immunologically-mediated skin reaction to [vancomycin](#), known as linear IgA bullous dermatosis (LABD), has been described ([picture 1](#)) [\[48-53\]](#). This entity may be confused with toxic epidermal necrolysis [\[54,55\]](#). In addition, a non-bullous, morbilliform variant of vancomycin-induced LABD has been reported [\[56\]](#). LABD can appear from one day to one month from the time of initial vancomycin administration. The reaction appears to be idiosyncratic and unrelated to peak or trough serum vancomycin levels.

The subepidermal blistering bullous lesions of LABD are difficult to distinguish from bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis, both on clinical and histopathologic grounds. Direct immunofluorescence is usually needed to confirm the diagnosis of LABD and can help exclude the other conditions. Linear IgA deposition at the dermal-epidermal junction of the basement membrane zone is the characteristic finding of LABD [\[57\]](#).

It is not known what prompts the formation of the autoantibodies, but it is possible

that an antigenic determinant on the drug cross-reacts with a component of the epidermal basement membrane [51].

Virtually all published case reports note resolution of LABD after discontinuation of [vancomycin](#). In situations where discontinuing vancomycin is not an option, [dapsons](#) or [prednisone](#) may be alternatives to stopping the antibiotic, based upon very limited experience [50].

Rare severe cutaneous reactions — Stevens-Johnson syndrome [58,59], exfoliative dermatitis [60], toxic epidermal necrolysis [61], extensive fixed drug eruption [62], and leukocytoclastic vasculitis [63] have all been described in association with [vancomycin](#) use in case reports. Early recognition and discontinuation of the drug are critical. Desensitization should never be performed following these reactions, as reexposure to the drug could result in a more severe or fatal recurrence of the reaction. (See "[Stevens-Johnson syndrome and toxic epidermal necrolysis: Clinical manifestations; pathogenesis; and diagnosis](#)".)

Hematologic — Hematologic manifestations of [vancomycin](#)-related reactions include leukocytosis, eosinophilia, neutropenia, and immune thrombocytopenia [64-69]. A case of agranulocytosis in a patient with renal insufficiency was also reported [9]. Vancomycin should be discontinued if these conditions develop. One report described resolution of vancomycin-induced neutropenia with substitution with structurally-related teicoplanin [70].

Drug-induced fever — Uncommonly, [vancomycin](#) has been implicated as a cause of drug-induced fever. In some instances, fever has occurred concomitant with vancomycin-elicited neutropenia [65,71]. Other reports have implicated vancomycin as a cause of drug-induced fever without confounding issues of coexisting neutropenia [44,45,72].

Renal — The potential of [vancomycin](#) to cause nephrotoxicity is controversial. (See "[Vancomycin dosing and serum concentration monitoring in adults](#)".) However, patients have been described who developed renal insufficiency due to acute interstitial nephritis in association with vancomycin administration [73]. Acute anuric renal failure has also been reported [74]. A biopsy proven case of acute tubular necrosis has also been reported, attributed to vancomycin and a single dose of aminoglycoside [75]. Vancomycin should be discontinued if these conditions are suspected.

USE OF TEICOPLANIN IN PATIENTS WITH VANCOMYCIN

HYPERSENSITIVITY — Teicoplanin, which is not available in the United States, is a newer glycopeptide antimicrobial with structural similarity to [vancomycin](#), similar efficacy in treating invasive beta-lactam resistant gram-positive infections, but with lower rates of adverse events, particularly nephrotoxicity and red man syndrome

[34,76]. There is only limited information about the safety of teicoplanin in patients with a previous hypersensitivity reaction to vancomycin.

- A retrospective series evaluated 117 patients who had drug-induced fever (24 patients), rash (77), both (8), or neutropenia (8) while receiving [vancomycin](#) and were switched to teicoplanin [71]. Clinical information and the development of drug fever, rash, or neutropenia with teicoplanin were determined by medical record review. Ten percent of patients developed fever, rash, or neutropenia in response to teicoplanin and there were no fatalities due to drug adverse reactions to teicoplanin. Of note, 50 percent of patients with neutropenia to vancomycin also developed neutropenia in response to teicoplanin. Thus, with the exception of patients with neutropenia, the majority tolerated teicoplanin.
- Recurrence of vasculitic rash was described in two patients treated with teicoplanin who had previously reacted to [vancomycin](#) [32].

SUMMARY AND RECOMMENDATIONS

Red man syndrome — The most common adverse reaction to [vancomycin](#) is "red man syndrome" (RMS), which is characterized by flushing, erythema, and pruritus, usually of the upper body. Chest and back pains and hypotension may also occur. (See '[Signs and symptoms](#)' above.)

- RMS is a rate-related infusion reaction that occurs more frequently at faster rates of administration. It is not a true allergic reaction. Other agents that also activate mast cells, such as opioids, muscle relaxants, and radiocontrast media, can predispose patients to developing RMS upon [vancomycin](#) infusion. (See '[Mechanism](#)' above and '[Predisposing medications](#)' above.)
- We do not empirically premedicate patients receiving [vancomycin](#) who have no history of previous RMS or have never received vancomycin, if the drug is to be administered as recommended (ie, at rates ≤ 10 mg/min or 1 gram over more than one hour). More rapid infusions should be avoided when possible. (See '[Prevention of initial reactions](#)' above.)
- In patients who require more rapid infusions of [vancomycin](#) (ie, at rates exceeding 10 mg/min or 1 gram over one hour), we recommend antihistamine premedication with at least an H1 antihistamine (**Grade 1B**). We suggest a combination of H1 and H2 antihistamines (**Grade 2C**). We administer the combination of [diphenhydramine](#) (50 mg orally) and [ranitidine](#) (150 mg orally) one hour before infusion, although the optimal regimen has not been determined. (See '[Prevention of initial reactions](#)' above.)
- RMS is treated by stopping the infusion. Further treatment depends upon the

severity of the reaction. The patient's medication list should be reviewed carefully to determine if other predisposing medications can be identified and discontinued. (See '[Management of acute RMS](#)' above.)

- For mild reactions (eg, flushing that is not bothersome to the patient), symptoms typically resolve in minutes and antihistamines are usually not necessary. We usually restart the infusion at one-half the previous rate. (See '[Management of acute RMS](#)' above.)
- For moderate reactions (eg, the patient is uncomfortable due to flushing or pruritus, but is hemodynamically stable and not experiencing chest pain or muscle spasm), we suggest treating with an H1 antihistamine (**Grade 2C**). We administer [diphenhydramine](#), (50 mg orally or intravenously). We usually restart the infusion at one-half the previous rate. (See '[Management of acute RMS](#)' above.)
- For severe reactions (eg, muscle spasms, chest pain, or hypotension), in addition to stopping the infusion, we suggest treatment with both H1 and H2 antihistamines (**Grade 2C**). We administer [diphenhydramine](#) (50 mg intravenously) and [ranitidine](#) (50 mg intravenously). IV fluids may be needed for hypotension. We suggest infusing any subsequent doses of [vancomycin](#) over four hours. (See '[Management of acute RMS](#)' above.)
- For patients with previous history of RMS who require [vancomycin](#) again, we recommend antihistamine premedication with at least an H1 antihistamine (**Grade 1B**). We suggest a combination of H1 and H2 antihistamines (**Grade 2C**). We administer the combination of [diphenhydramine](#) (50 mg orally) and [ranitidine](#) (150 mg orally) one hour before infusion and infuse each vancomycin dose over four hours.
- For patients with recurrent symptoms despite premedication and slow infusion rates, who absolutely require [vancomycin](#) in the future, we suggest desensitization (**Grade 2C**). Desensitization is traditionally used in IgE-mediated reactions, although the procedure has been applied successfully to severe RMS as well. (See '[Desensitization](#)' above.)

Anaphylaxis — Anaphylaxis in response to [vancomycin](#) administration is rare. Symptoms of anaphylaxis overlap with those of severe RMS, although wheezing, significant dyspnea, and angioedema are more suggestive of anaphylaxis. Multiple prior vancomycin courses should raise concern about the potential for IgE-mediated allergy ([table 2](#)). (See '[Clinical manifestations](#)' above.)

- If anaphylaxis is suspected, the infusion should be stopped immediately, and the patient treated with epinephrine ([table 3](#) and [table 4](#)). (See '[Acute management](#)' above.)

- Serum tests (histamine or tryptase) cannot reliably differentiate severe RMS from anaphylaxis. Skin testing for [vancomycin](#) is not validated, although a positive skin test at concentrations of 1 mcg/mL or lower is suggestive of drug allergy. (See ['Serum tests and skin tests'](#) above.)

- For patients who have developed anaphylaxis in response to [vancomycin](#), use of an equivalent alternative antibiotic should be considered initially. (See ['Use of alternate medications'](#) above.)

- For patients with serious infections that cannot be adequately treated with alternate antimicrobials, we suggest [vancomycin](#) desensitization (**Grade 2C**). (See ['Desensitization'](#) above.)

- Desensitization involves gradually reintroducing the culprit drug in serially increasing doses to induce a state of temporary clinical tolerance. There are several published protocols, although the optimal approach is not known. We suggest a rapid protocol that allows the patient to receive a full dose of [vancomycin](#) within several hours (**Grade 2C**). (See ['Desensitization'](#) above.)

- Other rare forms of [vancomycin](#) hypersensitivity include DRESS syndrome/DiHS, cutaneous reactions (eg, linear IgA bullous dermatosis), and renal disorders. The drug must be discontinued if these occur. Desensitization is not effective and may be dangerous. (See ['Other forms of hypersensitivity'](#) above.)

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GRAPHICS

Known histamine inducers that may prevent successful vancomycin desensitization

Antibiotics
Ciprofloxacin, vancomycin
Barbiturates
Narcotic analgesics*
Neuromuscular antagonists•
Quaternary amine
Succinylcholine
Benzyloisoquinolinium compounds
Atracurium, cisatracurium, doxacurium, mivacurium, tubocurarine
Propofol
Plasma expanders
Dextran, polygeline (Haemaccel)
Radiocontrast agents

* Fentanyl rarely induces histamine release.

• Steroidal neuromuscular antagonists cause little or no histamine release (ie, pancuronium, pipecuronium, rocuronium, vecuronium). *Reproduced with permission from: Wazny, LD, et al. Desensitization protocols for vancomycin hypersensitivity. The Annals of Pharmacotherapy 2001; 35:1458. Copyright ©2001 Harvey Whitney.*

Signs and symptoms of anaphylaxis

Skin:
Feeling of warmth, flushing [erythema], itching [may begin on palms and soles], urticaria, angioedema, morbilliform rash, and "hair standing on end" [piloerection]
Oral:
Itching or tingling of lips, tongue, or palate
Edema of lips, tongue, uvula, metallic taste
Gastrointestinal:
Nausea, abdominal pain [colic, cramps], vomiting [large amounts of "stringy" mucus], and diarrhea
Difficulty swallowing*
Respiratory:
Laryngeal - pruritus and "tightness" in the throat, dysphagia, dysphonia and hoarseness, and sensation of itching in the external auditory canals
Lung - shortness of breath, dyspnea, chest tightness, deep or repetitive cough, and wheezing
Nose - itching, congestion, rhinorrhea, and sneezing
Cardiovascular:
Feeling of faintness or dizziness; syncope, chest pain, palpitations, and/or hypotension (tunnel vision, difficulty hearing)
Neurologic:
Anxiety, apprehension, sense of impending doom, seizures, headache•, confusion
Ocular:
Periorbital itching, erythema and edema, tearing, and conjunctival erythema
Other:
Lower back pain due to uterine cramping in women

* Often occurs in association with throat tightness and other upper airway symptoms.

- Not common in anaphylaxis overall; however, reported in up to 30 percent of patients with exercise-induced anaphylaxis.

Rapid overview: Emergent management of anaphylaxis in adults

DIAGNOSIS IS MADE CLINICALLY:

Most common signs and symptoms are cutaneous (eg, urticaria, angioedema, flushing, pruritus). However, some patients have no skin findings.

Danger signs: Rapid progression of symptoms, respiratory distress (eg, wheezing, increased work of breathing, persistent cough, stridor), persistent vomiting, hypotension, dysrhythmia, chest pain, syncope

ACUTE MANAGEMENT:

The first and most important therapy in anaphylaxis is epinephrine. There are **NO absolute contraindications** to epinephrine in the setting of anaphylaxis.

Airway: Immediate intubation if evidence of impending airway obstruction from angioedema; delay may lead to complete obstruction; intubation can be difficult; cricothyrotomy may be necessary

Promptly and simultaneously, give:

IM Epinephrine (1 mg/mL preparation): Give aqueous epinephrine 0.3 to 0.5 mg intramuscularly, preferably in the mid-anterolateral thigh; can repeat every 3 to 5 minutes as needed. If symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion (see below).

Place patient in recumbent position, if tolerated, and elevate lower extremities

Oxygen: Give 6 to 8 liters per minute via face mask, or up to 100 percent oxygen as needed

Normal saline rapid bolus: Treat hypotension with rapid infusion of 1 to 2 liters IV; repeat as needed; massive fluid shifts with severe loss of intravascular volume can occur

Also consider administration of:

Albuterol: For bronchospasm resistant to IM epinephrine, give 2.5 to 5 mg in 3 mL saline via nebulizer; repeat as needed

H1 antihistamine: Give diphenhydramine 25 to 50 mg IV (for relief of urticaria and itching only)

H2 antihistamine: Consider giving ranitidine 50 mg IV

Glucocorticoid: Consider giving methylprednisolone 125 mg IV

Continuous non-invasive hemodynamic and pulse oximetry monitoring should be performed

TREATMENT OF REFRACTORY SYMPTOMS:

Epinephrine infusion: For patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion, 2 to 10 micrograms per minute by infusion pump. Titrate the dose continuously according to blood pressure, cardiac rate and function, and oxygenation, as assessed by continuous non-invasive monitoring.

Vasopressors: Patients may require vasopressors, given by infusion pump, with the doses titrated continuously according to blood pressure, cardiac rate and function, and oxygenation, as assessed by continuous non-invasive monitoring

Glucagon: Patients on beta-blockers may not respond to epinephrine and can be given glucagon 1 to 2 mg IV over 5 minutes, followed by infusion of 5 to 15 micrograms per minute

Rapid Overview: Emergent management of anaphylaxis in infants and children

DIAGNOSIS IS MADE CLINICALLY

Most common signs and symptoms: cutaneous (eg, urticaria, angioedema, flushing, pruritus) and vomiting

Danger signs: Rapid progression of symptoms, evidence of respiratory distress (eg wheezing, increased work of breathing, retractions, persistent cough, stridor), signs of poor perfusion*, dysrhythmia, syncope

ACUTE MANAGEMENT

The first and most important therapy in anaphylaxis is epinephrine. There are **no absolute contraindications** to epinephrine in the setting of anaphylaxis

Airway: Immediate intubation if evidence of impending airway obstruction from angioedema; delay may lead to complete obstruction; intubation can be difficult and cricothyrotomy may be necessary

IM Epinephrine (1 mg/mL preparation): Give epinephrine 0.01 mg per kilogram intramuscularly (maximum per dose: 0.5 mg), preferably in the mid-anterolateral thigh, can repeat every 3 to 5 minutes as needed. If signs of poor perfusion* are present or symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion (see below)

Place patient in recumbent position, if tolerated, and elevate lower extremities

Oxygen: Give 6 to 8 liters per minute via face mask, or up to 100 percent oxygen as needed

Normal saline rapid bolus: Treat signs of poor perfusion* with rapid infusion of 20 mL per kilogram; re-evaluate and repeat fluid boluses (20 mL per kilogram) as needed; massive fluid shifts with severe loss of intravascular volume can occur; monitor urine output

Albuterol: For bronchospasm resistant to IM epinephrine, give albuterol 0.15 mg per kilogram (minimum dose: 2.5 mg) in 3 mL saline inhaled via nebulizer; repeat as needed

H1 antihistamine: Give diphenhydramine 1 to 2 mg per kilogram (max 50 mg) IV; can give IM if symptoms are less severe

H2 antihistamine: Consider giving ranitidine 1 to 2 mg per kilogram (max 50 mg) IV

Glucocorticoid: Consider giving methylprednisolone 2 mg per kilogram (max 125 mg) IV

Hemodynamic and pulse oximetry monitoring should be performed continuously

TREATMENT OF REFRACTORY SYMPTOMS

Epinephrine infusion: Patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion at 0.1 to 1 microgram per kilogram per minute, titrated to effect and with constant hemodynamic monitoring

Vasopressors: Patients may require large amounts of IV crystalloid to maintain blood pressure; if response to epinephrine and saline is inadequate, dopamine (5 to 20 micrograms per kilogram per minute) can be given as continuous infusion, titrated to effect and with constant hemodynamic monitoring

* See the topic "Assessment of perfusion in pediatric resuscitation".

Desensitization protocol for vancomycin

Dose number	Dose* (mg)
1	0.005
2	0.010
3	0.020
4	0.040
5	0.080
6	0.160
7	0.320
8	0.640
9	1.25
10	2.50
11	5.00
12	10.00
13	20.00
14	40.00
15	80.00
16	160.00
17	320.00
18	640.00
19	1000.00

* Each dose was given in 50 mL of D5W infused over 15 minutes by infusion pump except the last dose, which was administered as 25 mL of 1 gm in 250 mL D5W over 15 minutes. The rest of the solution (1 gm in 250 mL D5W) was then infused at a rate of 200 mL/hr. *Reproduced with permission from: Villaviencio, AT, Hey, LA, Patel, D, Bressler, P. J Allergy Clin Immunol 1997; 100:853. Copyright © 1997 Mosby, Inc.*

Rapid Vancomycin desensitization protocol

Premedication: Diphenhydramine 50 mg iv and hydrocortisone 100 mg iv 15 minutes prior to initiation of protocol, then q6h throughout protocol

Infusion no.	Dilution	Vancomycin dose (mg)	Concentration (mg/mL)
1	1:10,000	0.02	0.0002
2	1:1000	0.20	0.002
3	1:100	2.0	0.02
4	1:10	20	0.2
5	standard	500	2.0

Preparation

1. Prepare a standard bag of 500 mg vancomycin in 250 mL NS or D5W; label as infusion no. 5, vancomycin 2 mg/mL.
2. Draw up 10 mL of the standard vancomycin 2-mg/mL preparation and place in 100-mL bag of NS or D5W; label as infusion no. 4, vancomycin 0.2 mg/mL.
3. Draw up 10 mL of the 0.2-mg/mL solution and place in a 100-mL bag of NS or D5W; label as infusion no. 3, vancomycin 0.02 mg/mL.
4. Draw up 10 mL of the 0.02-mg/mL solution and place in a 100-mL bag of NS or D5W; label as infusion no. 2, vancomycin 0.002 mg/mL.
5. Draw up 10 mL of the 0.002-mg/mL solution and place in a 100-mL bag of NS or D5W; label as infusion no. 1, vancomycin 0.0002 mg/mL.

Infusion rate directions

Initiate infusion rate at 0.5 mL/min (30 mL/h) and increase by 0.5 mL/min (30 mL/h) as tolerated every 5 min to a maximum rate of 5 mL/min (300 mL/h). If pruritus, hypotension, rash, or difficulty breathing occurs, stop infusion and reinfuse the previously tolerated infusion at the highest tolerated rate. This step may be repeated up to three times for any given concentration.

Upon completion of infusion no. 5, immediately administer the required dose of vancomycin in the usual dilution of NS or D5W over 2 h. Decrease rate if pt. tolerated dose. Administer diphenhydramine 50 mg po 60 min prior to each dose.

D5W: dextrose 5 percent in water; NS: NaCl 0.9 percent. *Reproduced with permission*

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Management of adverse reactions during desensitization

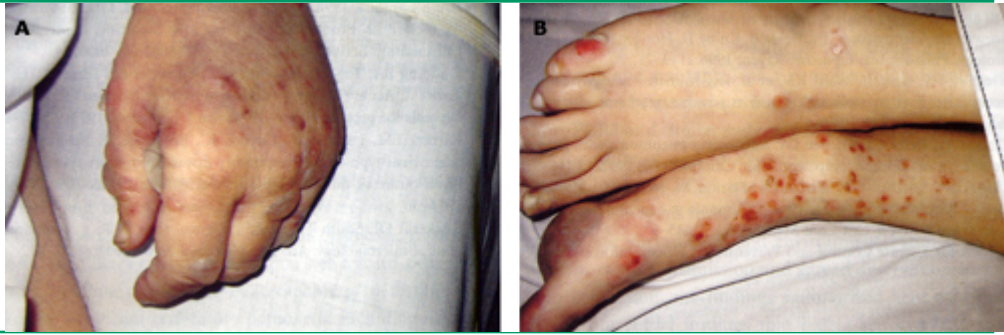
Reaction severity	Symptoms and signs	Management
Mild	Mild urticaria without hemodynamic instability, respiratory distress, or angioedema.	The last dilution tolerated without difficulty should be repeated and the protocol continued if no further reaction occurs.
Moderate	Chest tightness, diffuse hives, but no hemodynamic or airway compromise.	Administer 0.3 mL 1:1000 epinephrine (0.3 mg) intramuscularly. If the patient's symptoms resolve within 30 minutes, the last dilution tolerated without a reaction should then be repeated and the protocol continued if no further reaction occurs.
Moderate to severe	Diffuse wheezes, throat tightness.	Administer epinephrine as described above. Epinephrine can be repeated every 15 minutes if required. If the reaction is severe, 0.5-1.0 mg of 1:10,000 epinephrine can be given IV every 5 minutes. Consider intubation* If the symptoms subside quickly and if the antibiotic is considered to be absolutely necessary to adequately treat the patient, one half the dose of the last tolerated dilution• should be given with a physician at the bedside. Desensitization can then be continued if this dose is tolerated without reaction.
Severe	Hypotension, laryngeal edema with or without urticaria.	Treat with epinephrine as above, and give the following IV: 50 mg diphenhydramine Histamine H2 receptor blocker Corticosteroids, eg, 60mg methylprednisolone

The desensitization protocol must be discontinued.
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For example, if Dilution #4 (1×10^{-3}) concentration of the final dose) of Table 3 was the last tolerated dose, administer 0.5×10^{-4} concentration of the final dose in 50 mL normal saline.

* Intubation should be considered if laryngeal edema and/or severe bronchospasm leading to respiratory failure do not rapidly improve following the administration of epinephrine and antihistamines. Failure to maintain a patent airway and inability to maintain adequate oxygenation and ventilation are indications for intubation.

Skin lesions due to vancomycin hypersensitivity



Photographs of erythematous macules, vesicles, tense bullae, and erosions on the left hand (A) and tense bullae and erosions on the dorsal surfaces of the feet (B) in a 63- year old man with skin eruptions after vancomycin administration. *Reproduced with permission from: Clin Infect Dis 2004; 38:398. Copyright © 2004 University of Chicago Press.*

